analysis methods and demonstrate the method's superiority in inferring correct HMM topology and kinetic parameters. We then apply the method to DNA polymerase binding and replication to identify binding of multiple polymerases to a DNA overhang construct and to extract binding, dissociation, and polymerization kinetics. The presented statistical algorithm provides objective quantification of single-molecule trajectories and successfully identifies, segments, and analyses photophysical, dynamical, and stoichiometric 'regimes' within these trajectories. Our work illuminates important mechanisms in DNA replication and paves the way for experimental extension to studies of large complexes and molecular machines and to the field of single-molecule enzymology.

3030-Pos Board B800

Specification, Construction, and Exact Reduction of Finite State Transition System Models of Biochemical Processes

Scott M. Bugenhagen, Daniel A. Beard.
Medical College of Wisconsin, Milwaukee, WI, USA.

Biochemical reactions may be viewed as discrete event processes characterized by a finite number of states and transitions. These processes may be modeled as finite state transition systems where state transitions represent individual reaction events. The time-evolution of the state occupancy probabilities of such systems is described by the master equation. Since these systems often involve a large number of interactions, it can be difficult to construct the master equation for a model describing a system, and since the resulting models can involve a huge number of states, solving the associated master equation can be difficult or impossible. Here, we describe a method for the specification, construction, and reduction of finite state transition system models of biochemical processes using the symmetry and invariant manifold reduction techniques. The method allows a user to specify transition rules using an intuitive graphical representation, and to automatically construct the transition matrix of a differential equation characterizing exactly the dynamics of a model, with a potentially significant reduction in dimension when compared to the full master equation of the model. The application of the method to a biological process is illustrated by models describing a hypothetical ion-channel at several levels of complexity.

3031-Pos Board B801

Reported Cellphone Effects on Brain Energetically Consistent with Electrostriction

William J. Bruno[1,2].
[1]Los Alamos National Laboratory, Los Alamos, NM, USA, [2]New Mexico Consortium, Los Alamos, NM, USA.

Cellphone exposure reportedly alters brain EEG [1], blood flow [2] metabolism [3], and blood-brain barrier [4]. Others claim slight heating is the only plausible effect. We find deformation of soft tissue by electrostriction forces energetically possible. We consider a simple model of two hemispheres of fatty brain immersed in an aqueous fluid of higher dielectric constant. The polar fluid is attracted to regions of stronger electric field at the skull surface. The pressure pushing the hemispheres together could be transduced by pressure sensors between the hemispheres; cycling of the pressure might also cause damage akin to mechanical fatigue. Such forces are small but normally vanish due to neutral buoyancy. Assuming very soft tissue (rat brains soften with age) and published tissue permittivities, we find the energy difference $\Delta U = (\varepsilon_1^{-1} - \varepsilon_2^{-1})\ S\ V / 2c$ from displacing a volume V of 1 cc of fluid by a nearby cell tower or wi-fi computer causing incident power density S of one mW/m^2 creates deformation that slightly exceeds thermal noise. Data modulations cannot be transduced by the slow-moving fluid, but pulse modulations (used to reduce mobile devices' duty cycles) can. Blood also has a higher dielectric constant than brain, so there would be a force on the blood brain barrier.

Sharp et al. [5] similarly invoked photon pressure as the basis for microwave hearing [6]. Lower frequency fields are better shielded by the skin, but the effect might explain headache from a pulsed low-frequency electric field [7].

1. Schmid+, J. Sleep Res. DOI: 10.1111/j.1365-2869.2011.00918.x (2011).
2. Huber+, J. Sleep Res. 11:289 (2002).
3. Volkow+, JAMA 305:808 (2011).
4. Salford+, Environ. Health Perspect. 111:881 (2003).
5. Sharp+, Microwave Theory & Techniques, IEEE Trans. on, 22:583 (1974).
6. Frey+, Science 181:356 (1973).
7. Marino+, Int. J. Neurosci. doi:10.3109/00207454.2011.608139 (2011).

3032-Pos Board B802

Global Sensitivity Analysis of Arrhythmic Risk Biomarkers in Cardiac Single Cell Models

Anna A. Sher[1], Paul Carter[1], Blair Bethwaite[2], Denis Noble[1], David Abramson[2], David J. Gavaghan[1].
[1]Oxford University, Oxford, United Kingdom, [2]Monash University, Melbourne, Australia.

Global sensitivity analysis is critical in understanding the role of ionic currents variability in modulating cellular electrophysiological properties of ventricular myocytes as well as in assessing the cardiac single cell arrhythmic risk biomarkers. This work involves a systematic investigation into the sensitivity of various preclinical cellular biomarkers of arrhythmic risk to changes in ionic current conductances and kinetics. We compare local and global sensitivity analysis approaches. The nonlinearity of the system is confirmed to play an important role when considering the effect of parameters on markers that involve information from different frequencies. In the case of such biomarkers as action potential duration (APD), maxima Cai and Nai concentrations, we find no significant changes in the overall order of the parameters' significance between local and global sensitivity studies. However, even for these single frequency markers we are able to give a more precise relative contribution of each parameter. Importantly, in the case of maximum S1-S2 slope marker, which integrates the information across a spectrum of frequencies of electrical stimuli, we find significant changes in the order of parameters as compared to the previously used methods for studying the sensitivity of cellular biomarkers. Moreover, the models consistently identify the L-type Calcium current (ICaL) as one of the dominant currents affecting the plateau of the action potential. Furthermore, in consistence with experimental data, the simulation results show that variation in conductances and kinetics of other channels does not affect the significance of ICaL's contribution. We demonstrate the critical role of global (vs local) sensitivity analysis in providing insights into the sensitivity of preclinical biomarkers, and hence mechanisms of repolarization and their rate dependence.

3033-Pos Board B803

Low Temperature Matrix Isolation IR-Spectroscopy and Quantum Chemical Study of β-Alanine Structure

Daryna Smyrnova[1], Stepan Stepanian[2].
[1]The Katholieke Universiteit Leuven, Leuven, Belgium, [2]B.Verkin Institute for Low Temperature Physics and Engineering of the National Academy of Sciences of Ukraine, Kharkiv, Ukraine.

In this study we have focused on conformational structure of the β-alanine molecule isolated in low-temperature argon matrices. The main purpose was to determine the set of the β-alanine conformers, which can occur in the matrices. Matrix isolation FTIR-spectroscopy was combined with quantum chemical calculations performed by the MP2 and DFT(B3LYP) methods using the aug-cc-pVDZ and aug-cc-pVTZ basis sets. Gibbs free energies of the β-alanine conformers also were calculated at the CCSD(T)/CBS level of theory.

Totally 21 β-alanine conformers were found at the MP2/aug-cc-pVDZ level of theory. But 10 of them are separated from lower energy conformers by low energy barriers and they can not present in the matrixes. High-resolution FTIR spectra were registered for the samples immediately after deposition as well as for the samples which were UV irradiated or annealed to 25K. Both the UV irradiation and the matrix annealing result in redistribution of the band intensities in the FTIR spectra. It allows us to distinguish spectral bands of different β-alanine conformers. Assignment of the spectral bands was performed based on calculated vibrational spectra of the β-alanine conformers. As a result we detected presence of 4 β-alanine conformers in the Ar matrices. Further data about β-alanine conformational structure can be used in molecular dynamics simulations and also they can be useful for searching of β-alanine in the interstellar space.

Key words: β-alanine, matrix isolation, quantum chemical calculations.

3034-Pos Board B804

Atomistic Simulation Studies of the Permeation of Organic Molecules Through Lipid Membranes

Zhaleh Ghaemi Bafghi[1], Alessandro Laio[1], Paolo Carloni[2].
[1]SISSA(Scuola Internazionale Superiore di Studi Avanzati), Trieste, Italy, [2]German Research School for Simulation Sciences, Julich, Germany.

For drugs with intracellular targets the process of permeation through the membrane is of fundamental importance (A. Malkia, et al., Euro J of Pharm

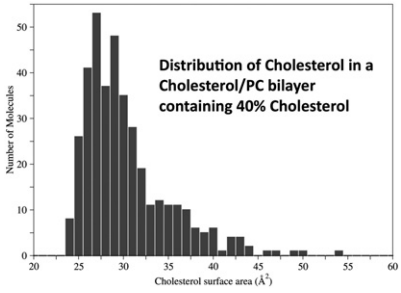
Scien, 23,13-47, 2004). Usually the rate of this process is predicted using QSAR or other knowledge-based predictors (R Gozalbes, et al., Bioorganic & Med Chem,19, 2615-2624, 2011). However, this approach is not always accurate. Moreover, it does not provide the atomistic details of the process, and thus its prediction cannot be directly exploited to rationally design drugs with higher permeation rate. We developed a protocol for studying the permeation of small organic molecules (e.g. drugs) through lipid membranes by atomistic simulations. This protocol allows computing accurately the permeability coefficient, and provides a detailed atomistic picture of the process. The approach is based on an enhanced sampling technique, bias exchange metadynamics (S. Piana and A. Laio, J Phys Chem B, 111, 4553-4559, 2007), that allows deriving from atomistic simulations a multidimensional free energy landscape and an accurate kinetic model describing the transitions between the relevant metastable states of the system (F Marinelli, et al., Plos Comp Biol, 5, e1000452, 2009). As a benchmark, we applied this protocol on the permeation of ethanol through palmitoyloleoylphosphatidylcholine (POPC) membrane. We are applying the same procedure to study the permeation of two anti-HIV drugs where unbiased simulation of the permeation process is not possible.

3035-Pos Board B805

A New Monte Carlo Method for Exploring the Surface Area, Volume and Voids of Molecules in Protein Containing Lipid Bilayers with Atomistic Detail

Liming Qiu[1], Sara Y. Cheng[2], Kwan H. Cheng[3], Mark Vaughn[1].
[1]Texas Tech University, Lubbock, TX, USA, [2]UC Berkeley, Berkeley, CA, USA, [3]Trinity University, San Antonio, TX, USA.

The distribution statistics of the surface area, volume and voids of biological molecules are important parameters to characterize the structures of lipid membranes in the field of atomistic MD simulations. Traditional surface area calculation methods are mostly based on various assumptions of the thickness of the membrane and the volumes of certain molecules. However, those methods usually lead to different surface area estimations and fail to estimate the voids. In the presence of protein, those methods are not applicable due to the presence of the conformal annular lipids surrounding the protein. We have therefore developed a new Monte Carlo method that is capable to calculate the distributions, averages and kinetics of surface area, volume and void space of the lipid or protein molecules in protein containing lipid bilayers obtained from MD simulations at the atomistic scale. We have successfully validated this method using an ordered hard-sphere test system. Results of the structural parameters of the annular lipids in close proximity to the embedded protein and the non-annular lipids using this new method will be presented.



3036-Pos Board B806

Extracting Kinetic Models from Single Molecule Experiments by Direct Inference

Steve Presse[1], Julian Lee[2], G.J. Peterson[1], Justin MacCallum[3], Ken A. Dill[3].
[1]University of California, San Francisco, San Francisco, CA, USA, [2]Soonsil University, Seoul, Korea, Republic of, [3]Stony Brook University, Stony Brook, NY, USA.

The enterprise of kinetic model-building has been a key route to insight in biophysics. An explosive growth in single molecule experiments is yielding a wealth of information on time-ordered sequences of inter-conversion between conformational states. Current strategies for model building- Markov models - often start by picking a model topology, de-noise the data according to this topology and use the data to fit the rates of the model by maximum likelihood methods. This can bias the analysis and waste data by forcing it onto a particular model. Other methods, based on maximum entropy, do not waste data or bias the analysis though they only extract rate distributions from data not the entire kinetic model. We will discuss a method we are developing which, while based on maximum entropy, extracts the full model from single molecule time traces in an unbiased fashion. We do this by numerically extracting a quantity we call a memory kernel from data. The structure of the kernel tells us whether the data warrants a simple Markov model and, if so, towards which Markov model the data naturally tends towards within uncertainty bars and without wasting data. We apply this method to real single molecule data as well as simulated test cases.

3037-Pos Board B807

Modeling Fluorescence Observables, Particularly for FRET Experiments, using Markov Chain Analysis of Molecular Dynamics and Quantum Mechanics Simulations

Amy L. Speelman[1], Aurora Muñoz-Losa[2], Katie L. Hinkle[1], Darren B. VanBeek[1], Benedetta Mennucci[2], **Brent P. Krueger**[1].
[1]Hope College, Holland, MI, USA, [2]Università degli Studi di Pisa, Pisa, Italy.

We present a new method for simulating fluorescence observables, particularly those related to bulk and single-molecule fluorescence-detected resonance energy transfer (FRET) experiments. In this method, a molecular dynamics (MD) simulation is used to sample configuration space and quantum mechanics (QM) calculations are used to estimate the electronic coupling between the donor and acceptor probes for snapshots along the MD trajectory. A Markov chain method is used to sample the resulting electronic coupling trajectory allowing accurate simulation of any desired fluorescence observables, such as FRET efficiency histograms or time-resolved donor fluorescence decays. The Markov chain results will be compared with the results of simple histogram and averaging schemes showing that the Markov chain is the only one that yields realistic results in well known examples such as the rapid diffusion limit. This combination of computational methods also avoids some pitfalls of traditional FRET analysis such as the kappa-squared and the ideal dipole approximations. Because the simulation results can be compared directly with experimental observables, this method may allow more detail to be derived from experiment than is traditionally possible.